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ORIGINAL ARTICLE

Early treatment response evaluated by a clinical scoring system correlates with the prognosis of pulmonary tuberculosis patients in Ethiopia: A prospective follow-up study

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Abstract

Background: In resource-limited settings the monitoring of tuberculosis (TB) patients is challenging, and early identification of TB patients with a high mortality risk is important. The aim of this study was to investigate prospectively whether early changes in a clinical scoring system (TB score) can predict treatment outcome in Ethiopian patients with pulmonary tuberculosis. *Method:* TB patients ($n = 250$) and blood donors ($n = 82$) were recruited prospectively at Gondar University Hospital, Ethiopia. Clinical scoring was performed using an interview-based questionnaire and clinical examination. *Results:* Among TB patients (53.6% of whom were HIV co-infected) the median TB score declined from week 0 to week 2 (8 (interquartile range (IQR) 6–9) vs 4 (IQR 2–6)) and dropped to a low level at week 8, which was still significantly higher than that found in blood donors (2 (IQR 1–4) vs 0 (IQR 0–1), $p < 0.0001$). Patients who died had a significantly higher TB score at week 0, week 2, and week 8 than survivors. Mortality was associated with a failure to achieve a decrease greater than 25% in the TB score at 2 weeks. Baseline CD4 + cell counts (< 200 cells/mm^3) were associated with mortality but not with initial TB score results. *Conclusions:* The TB score was increased during the first 2 months of treatment among patients who died. Failure to achieve a greater than 25% decrease in TB score after 2 weeks of treatment was associated with increased mortality. Repeated clinical scoring during the intensive phase of TB treatment could be useful to identify high-risk patients.

Keywords: *Tuberculosis, HIV, TB score, outcome, mortality*

Introduction

The impact of tuberculosis (TB) is greatest in low-income countries, both with regard to the burden of new cases and deaths due to TB [1]. Hitherto, no satisfactory method exists that can identify patients at high risk of death during TB treatment. In resource-limited settings, it is difficult to monitor TB patients during treatment and still no surrogate marker for treatment response is accessible for smear-negative pulmonary TB patients. This is especially problematic in the setting of HIV co-infection, in which such manifestations are more common [2].

In this regard, laboratory biomarkers and radiological follow-up have been shown to be both insensitive and technically demanding [3]. Therefore, there is a need to develop cost-effective and simple parameters for predicting treatment outcome early.

A previous retrospective study in TB patients from Guinea-Bissau showed that clinical signs of immune deficiency (such as oral Candida infection or oral hairy leukoplakia and diarrhoea), low body mass index (BMI), and low mid-upper arm circumference (MUAC) were predictors of increased mortality [4]. A recent systematic review also found that

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HIV co-infection, advanced immunosuppression, smear-negative disease, and malnutrition were risk factors for mortality [5]. A previous meta-analysis has shown that it is possible to identify individuals with suspected TB using a simplified screening algorithm based on clinical symptoms [6].

Researchers from Guinea-Bissau have proposed a scoring system (TB score) based on clinical parameters for field use in highly endemic areas, and have presented a retrospective evaluation of a cohort of 698 patients treated for TB with regard to final outcome [7]. They showed that the score at the time of TB diagnosis could identify patients with a high risk of mortality [7]. Data on the performance of the TB score from other settings and its correlation with HIV co-infection and CD4 + cell counts are limited. Repeated scoring during early treatment could increase the capacity of the TB score to identify patients at risk of mortality, as the majority respond with a clinical improvement within 2 weeks [1].

The aim of our study was to investigate prospectively whether early changes in TB scoring results can predict treatment outcome in Ethiopian patients with pulmonary tuberculosis and whether the TB score is influenced by HIV co-infection and CD4 + cell levels.

Materials and methods

Study participants

Adult outpatients with pulmonary TB were prospectively recruited at the directly observed treatment short-course (DOTS) clinic of Gondar University Hospital, Ethiopia between June 2007 and January 2009. Inclusion criteria were a diagnosis of smear-positive or smear-negative pulmonary TB, age between 18 and 65 y, and consent to HIV testing. Hospitalized patients, cases with isolated extrapulmonary tuberculosis, and patients already taking anti-TB treatment were excluded. Smear-positive pulmonary TB was defined as a patient with at least 2 sputum specimens positive for acid-fast bacilli (AFB) by microscopy, or a patient with 1 positive sputum specimen and chest radiographic abnormalities consistent with active pulmonary TB [8]. Smear-negative pulmonary tuberculosis was defined as symptoms suggestive of TB with 3 sputum smear samples negative for AFB, radiographic abnormalities consistent with pulmonary TB, and a lack of clinical response to 1 week of broad-spectrum antibiotic therapy [8]. All patients received 2 months of daily directly observed treatment with ethambutol, isoniazid, rifampicin, and pyrazinamide, followed by a 6-month continuation phase with isoniazid and ethambutol, in accordance with the Ethiopian guidelines in practice at the time of the study. Treatment was provided free of charge and no interruptions in the drug supply were recorded during the study period. For comparison, HIV-seronegative adults without signs of active TB were recruited from blood donors at the blood bank, Gondar University Hospital. TB scoring including the clinical examination was performed by the 2 specially trained nurses at the DOTS centre at week 0 before the patients had started TB treatment, at week 2, and at week 8. Both patients and controls provided written informed consent. The study was approved by the Ethics Review Committee at the University of Gondar, Ethiopia and by the Regional Ethics Review Board, Linköping, Sweden.

Laboratory examinations

Sputum smear microscopy was repeated for all patients with positive sputum smears at baseline and at the end of months 2, 5, and 7 of treatment to define the treatment outcome category [8]. CD4 + cell counts were measured within 2 weeks of treatment initiation for all patients. HIV testing was done at the hospital voluntary counselling and testing clinic (VCT) or at the DOTS clinic as part of the provider-initiated HIV counselling and testing programme (PIHCT), according to the hospital routine, using HIV rapid test kits (Determine® HIV-1/2 Ag/Ab Combo (Orlando, FL, USA); Capillus (Trinity Biotech USA Inc., NY, USA); Unigold (Trinity Biotech USA Inc., NY, USA)). HIV-positive patients were referred to the hospital HIV clinic for further assessment and were managed according to the World Health Organization (WHO)-based Ethiopian national guidelines for antiretroviral treatment (ART) at the time of the study. The aim was that ART should be started as early as possible in TB patients with profound immune suppression (CD4 counts < 50 cells/mm^3), and in HIV-infected patients with a CD4 count > 50 cells/mm^3, as soon as possible and primarily after the intensive phase of anti-TB treatment. CD4 + cell counts were analyzed using the FACSCount (BD Biosciences, San Jose, CA, USA).

TB score and clinical outcome data

Clinical scoring was performed according to Wejse et al. [7] including the variables: cough, haemoptysis, dyspnoea, chest pain, night sweating, anaemic conjunctivae, tachycardia (≥ 100/min), lung auscultation (any abnormal findings), axillary temperature ≥ 37.0°C, body mass index (BMI) ≤ 18 kg/m^2, BMI ≤ 16 kg/m^2, MUAC ≤ 220 mm, and MUAC ≤ 200 mm. Each variable contributes 1 point and the maximum score is 13. Based

on TB score results the patients were divided into 3 severity classes as previously described [7]: severity class I with a TB score of 0–5, severity class II with a TB score of 6–7, and severity class III when the TB score is ≥ 8. Treatment outcome categories were recorded for all patients at the end of treatment according to WHO definitions (cured, treatment completed, treatment failure, died, defaulted, and transferred out) [8,9]. As per WHO definitions for TB treatment outcome, all-cause mortality as well as other outcomes were registered in the DOTS register. If a patient failed to turn up for treatment, a tracer tried to find the patient by contacting relatives or friends by domiciliary visits and treatment outcome was then registered.

Statistics

In order to detect a minimally clinical important difference of 1.1 TB score points [7] of the TB patients at week 8 compared to the blood donors, 80 blood donors were needed at a power of 80% (alpha 0.05). Moreover, we assumed that a sample size of 250 TB patients (including a 10% loss to follow-up) was needed in order to detect a mortality difference from the expected 8% to 18% in the patients who did not show a decrease in the TB score of $>25\%$ between baseline and week 2, on the assumption of a 10% overall mortality and an estimated fraction of 20% not reaching a $<25\%$ decrease between baseline and week 2. Data are presented as the median and interquartile range. The data were analysed using Fisher's exact test for categorical variables and Wilcoxon and Mann–Whitney tests for continuous variables. A *p*-value below 0.05 was regarded as statistically significant. In a multiple logistic regression model applying mortality as the dependent variable (STATISTICA software package; StatSoft, Tulsa, USA), age, sex, HIV, presence of ART treatment, and CD4 + cell counts (<200 cells/mm^3) were included in the final analysis.

Results

Patient characteristics

Baseline characteristics of the 250 study participants and the 82 blood donors are shown in Table I. The main reason for exclusion was hospitalization of smear-negative patients (264/446 excluded patients); a flow chart of patients is shown in Figure 1. The HIV co-infection rate was slightly although not significantly higher in smear-negative than in smear-positive patients (59.0% (63/107) vs 50.0% (71/143), $p = 0.22$). Among the 250 patients, excluding defaulters and patients who died or who were transferred out, the TB score was not registered for 9 patients at week 2 and 22 could not be assessed at week 8 (Figure 1, Table II).

Treatment outcome

The final TB treatment outcome according to WHO was recorded in 248 of the 250 patients. Among the 248 patients, 17 (7%) died, 173 (70%) were cured and/or completed treatment, 33 (13%) were transferred out, and 25 (10%) were defaulters. The all-cause mortality was higher among HIV-positive TB patients (9.8%, 13/132) than HIV-negative TB patients (3.4%, 4/116; $p = 0.039$). The treatment outcomes are summarized in Table II. Although the exact time of death could not be defined, 11/17 patients (64.7%) died within 8 weeks.

Association between longitudinal TB score results and treatment outcome

Overall, a decline in TB score was observed from week 0 to week 2 (data presented as median (interquartile range (IQR)): 8 (6–9) vs 4 (2–6), $p < 0.0001$). During further follow-up, the TB score continued to decline to a low level at week 8; however, the score results were still significantly higher at this time point than those observed in blood donors (2 (1–4) vs 0 (0–1), $p < 0.0001$). We found no difference in the TB score between a successful clinical response (cured and treatment completed) vs an unfavourable response (died or defaulted) at baseline (8 (6–9) vs 8 (6–10); excluding patients transferred out). However, there was a significant difference in the TB score among these groups at week 2 (4 (2–5) vs 5 (2–7), $p = 0.031$) and at week 8 (2 (0–4) vs 5 (2–6), $p < 0.0001$). Moreover, we observed a significantly higher TB score at week 0 (9 (7–10) vs 8 (6–9)), week 2 (7 (5–8) vs 4 (2–5)), and at week 8 (5 (4–7) vs 2 (0–4)) among patients who died compared to those who achieved cure or treatment completion (Table II). Mortality was associated with a failure to achieve a 25% decrease in TB score at week 2 ($p = 0.027$). The kinetics of the TB score in this group, as well as in smear-positive and smear-negative patients, is presented in Figure 2. The majority who died during follow-up were classified as severity class III (70.6%) at baseline compared to those who were cured or completed treatment (52.0%) (Table III). Based on receiver operating characteristic curve (ROC) analysis (data not shown), a TB score cut-off of 9 could predict the risk of death with a sensitivity of 41% and a specificity of 78%, which is similar to those reported elsewhere [7].

Table I. Baseline characteristics of study participants.

	HIV-pos TB[a] ($n = 134$, 53.6%)	HIV-neg TB ($n = 116$, 46.4%)	Reference group ($n = 82$)
Age, y; median (IQR)	30 (26–37)	24 (20–28)	27 (23–36)
Males, *n* (%)	63 (47)	70 (60)	78 (95)
Smear-positive, *n* (%)	71 (53)	72 (62)	ND
CD4 + cell count cells/mm^3; median (IQR)	157 (80–245) ($n = 96$)	501 (390–664) ($n = 90$)	ND
TB score week 0; median (IQR)	8 (6–9)	8 (6–9)	0 (0–1)[b]

HIV-pos, HIV-positive; HIV-neg, HIV-negative; TB, tuberculosis; ND, not determined; IQR, interquartile range.

[a]The data on gender was missing for 1 HIV-positive TB patient.

[b]The HIV-positive and HIV-negative TB patients versus the reference group, $p < 0.0001$.

Association between TB score results and treatment outcome with regard to HIV serostatus and CD4 + cell counts

In a multivariate regression model, mortality was associated with an increased TB score (categorized 0–5, 6–9, and ≥ 10) at week 0 (odds ratio 3.4, 95% confidence interval 1.2–10.0, $p = 0.023$; Table IV) after adjusting for age, sex, HIV, presence of ART, and CD4 + cell counts (< 200 cells/mm^3). No difference was observed in the TB score at baseline (8 (6–10) vs 8 (6–9)), week 2 (4 (2–6) vs 4 (3–6)), or at week 8 (2 (0–4) vs 2 (1–4)) between HIV-positive and HIV-negative individuals. The TB score was 8 (6–9) among the HIV-negative TB patients with available CD4 cell results (90/116 patients). In HIV-positive TB patients, the median TB score was 8 (6–10) (data available for 96/134 patients, where 59/96 individuals had a CD4 + cell count < 200 cells/mm^3 (TB score 8 (6–9)). No correlation was found between the baseline TB score and the CD4 + cell count, either overall or in HIV-positive subjects. However, the patients who died (4 HIV-negative and 13 HIV-positive) had lower CD4 + cell counts at baseline compared to the patients who completed treatment and the patients who were cured (133 (85–260) vs 339 (158–521) cells/mm^3, $p = 0.025$). Regarding ART, 40% (54/134) of the HIV-positive patients were on ART during TB treatment. Almost half of them, 48.1% (26/54), had already initiated ART before they started TB treatment and the median time of ART initiation after TB treatment was 114 days.

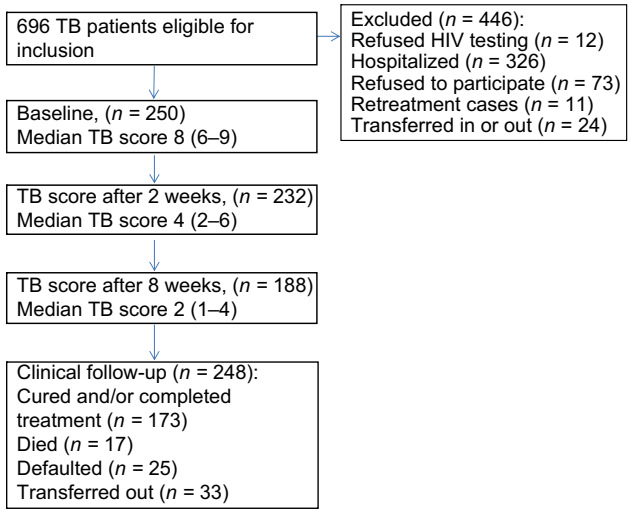

Figure 1. Flow chart of patients.

Discussion

In this study, we prospectively evaluated a clinical scoring system (TB score) during the intensive phase of treatment in a cohort of Ethiopian pulmonary TB patients [7]. The majority of patients showed a significant decline in the TB score results at 2 weeks after starting TB treatment, but the levels remained higher at week 8 than those found in the controls. A significantly increased TB score at week 0 and the absence of a decline in score results by more than 25% at 2 weeks were both associated with increased mortality. This suggests that repeated clinical scoring during the initial 8 weeks of TB treatment could be of value in routine practice to objectively identify high-risk patients. The early identification of TB patients at risk of a poor outcome might be important in high endemic areas in order to initiate targeted interventions such as hospital admission, additional diagnostic investigations, and intensified follow-up. Further research in this field has recently been called for [10] and additional prospective studies are needed to confirm that interventions based on a clinical scoring system such as the TB score have an impact on the TB-associated mortality.

The highest mortality rate was found in HIV-positive patients (13/134) and in particular in patients with a low baseline CD4 + cell count. Indeed, HIV infection appears to be the dominant risk factor for mortality among Ethiopian TB patients, and clinical

Table II. Association between median TB score results and treatment outcome.

	All TB patients ($n = 250$)[a]	Cured and treatment completed ($n = 173$, 70%)	Died ($n = 17$, 7%)	p-Value[b]	Transferred out ($n = 33$, 13%)	Defaulters ($n = 25$, 10%)	Not cured[c] ($n = 42$, 17%)	p-Value[d]
Males, n (%)[e]	133 (53.2)	78 (45.1)	14 (82)	0.0029	27 (82)	12 (48)	26 (62)	0.42
Age, y; median (IQR)	28 (23–35)	27 (21–35)	27 (25–32)	0.79	28 (25–37)	28 (24–36)	28 (25–33)	0.59
CD4 + cell count, week 0, cells/mm^3; median (IQR) ($n = 187$)	320 (142–518)	339 (158–521)	133 (85–260)	0.025	383 (147–572)	326 (119–495)	182 (86–470)	0.073
HIV-positive, n (%)	134 (53.6)	85 (49.0)	13 (76.5)	0.027	19 (58)	15 (60)	28 (67)	0.030
Smear-positive, n (%)[f]	143 (57.2)	104 (60.0)	7 (41)	0.11	12 (36)	18 (72)	25 (60)	0.54
TB score, week 0; median (IQR)	8 (6–9) ($n = 250$)	8 (6–9) ($n = 173$)	9 (7–10) ($n = 17$)	0.040	8 (7–10) ($n = 33$)	7 (6–10) ($n = 25$)	8 (6–10) ($n = 42$)	0.18
TB score, week 2; median (IQR)	4 (2–6) ($n = 232$)	4 (2–5) ($n = 164$)	7 (5–8) ($n = 13$)	< 0.0001	4 (3–6) ($n = 32$)	4 (1–5) ($n = 22$)	5 (2–7) ($n = 35$)	0.014
TB score, week 8; median (IQR)	2 (1–4) ($n = 188$)	2 (0–4) ($n = 151$)	5 (4–7) ($n = 6$)	< 0.0038	2 (1–3) ($n = 24$)	2 (1–5) ($n = 5$)	5 (2–6) ($n = 11$)	0.011

TB, tuberculosis; IQR, interquartile range.
[a]Outcome could not be determined in 2 HIV-positive TB patients.
[b]Cured and treatment completed versus patients who died.
[c]Not cured includes patients who died or defaulted.
[d]Cured and treatment completed versus patients who died or defaulted (not cured).
[e]Gender was not noted in the study record in 1 case.
[f]No treatment failures were recorded among smear-positive patients.

Figure 2. Kinetics of the TB score. Data are presented as medians, and error bars indicate the interquartile range. The kinetics of smear-positive (filled squares) and smear-negative (unfilled squares) TB patients, as well as patients exhibiting a $> 25\%$ decrease (unfilled triangles) and a $< 25\%$ decrease in the TB score from week 0 to week 2, are illustrated.

scoring and close monitoring should be prioritized for this group. It is well known that HIV-positive patients with TB have a high mortality risk [11,12]. A number of reasons contribute to this, including more severe disease, delayed diagnosis due to atypical presentation, co-existing opportunistic infections, delayed ART initiation, advanced immunodeficiency, and TB drug resistance. Despite the absence of drug susceptibility testing in this study, no treatment failure case was detected, which indicates a relatively low level of drug resistance.

Our study has several limitations, including that survival at the end of treatment could not be assessed for a high proportion of patients (60/250; 24%). Moreover, the specific cause and time of death could not be determined. It is possible that there could have been undetected deaths in the defaulting group (10%) and to a lesser extent among the patients who were transferred out [13]. To take this into consideration, default was considered an unfavourable response in the analysis of favourable vs unfavourable clinical response in relation to the TB score [14].

Although the national WHO-based strategy was used, another limitation of this study is that the smear-negative TB patients were not confirmed by culture and that drug susceptibility testing was not performed. However, the external validity of our results is still likely to be high as the setting is similar to where most TB patients are diagnosed and treated. Moreover, a treatment response in relation to the TB score was observed in the majority of smear-negative TB patients at a similar rate as for the smear-positive TB patients, which indicates a treatment response to the anti-TB therapy. Our study could not determine whether the initiation of ART during TB treatment

Table III. Association with treatment outcome according to the 3 severity classes of the TB score at week 0.

	Severity class I TB score 0–5	Severity class II TB score 6–7	Severity class III TB score ≥ 8
Cured or treatment completed week 0, *n* (%)	29 (16.8)	54 (31.2)	90 (52.0)
Died, *n* (%)	0 (0)	5 (29.4)	12 (70.6)
Defaulted, *n* (%)	5 (20.0)	9 (36.0)	11 (44.0)
Transferred out, *n* (%)	6 (18.2)	8 (24.2)	19 (57.6)
Not cured, *n* (%)[a]	5 (11.9)	14 (33.3)	23 (54.8)

TB, tuberculosis.
[a]Not cured includes patients who died or defaulted.

was associated with decreased mortality and was not primarily designed for that purpose.

A major benefit of the TB score is that it provides a simple tool for standardized evaluation of early clinical improvement in TB patients in high endemic areas. Early monitoring of patients with the TB score in the first 2 months of treatment could facilitate the identification of patients at high risk of a poor clinical outcome. This relatively simple clinical score could provide an objective tool for healthcare workers to identify high-risk patients. The TB score has demonstrated good inter- and intra-observer variability in an Indian setting and is easy to learn and to monitor [15]. The clinical evaluation can quickly be carried out without using expensive diagnostic tools and could be suitable for follow-up in clinical trials [7]. However, the scoring system needs further development to improve its capacity to predict clinical outcomes, especially with regard to HIV co-infection and parameters that are relevant in such patients. Furthermore, the definition of cut-off levels for practical use to pin-point high-risk patients needs to be explored in future studies, as well as how to implement the scoring algorithm at different levels of the healthcare system.

In conclusion, our study shows that the TB score can predict mortality among Ethiopian patients, and it may have a role in the follow-up of TB patients; this could be of use to target interventions and as a tool for evaluation in clinical trials.

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Table IV. Multivariate logistic regression analysis of the association between TB score and mortality at baseline adjusted for age, sex, HIV, ART, and CD4 count.

	Mortality			Univariate		Multivariate	
Parameter	*N*	*n*	%	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age, y							
≤28	137	9	6.6	1.00		1.00	
>28	109	8	7.3	1.13 (0.42–3.04)	0.813	0.75 (0.19–2.92)	0.680
Gender							
Female	131	14	10.7	1.00		1.00	
Male	116	3	2.6	0.22 (0.06–0.80)	0.021	0.29 (0.07–1.23)	0.092
HIV							
No	116	4	3.4	1.00		1.00	
Yes	132	4	3.0	3.06 (0.96–9.71)	0.058	3.52 (0.47–26.46)	0.220
ART treatment							
No	194	12	6.2	1.00		1.00	
Yes	54	5	9.3	1.55 (0.52–4.63)	0.433	0.76 (0.17–3.30)	0.711
CD4 count							
≥200	120	4	3.3	1.00		1.00	
<200	64	9	14.1	4.75 (1.39–16.22)	0.013	2.53 (0.50–12.87)	0.263
TB score week 0							
0–5	40	0	0	1.00		1.00	
6–9	150	10	6.7	2.68 (1.14–6.28)		3.45 (1.19–9.99)	
≥10	58	7	12.1	7.17 (1.30–39.47)	0.024	11.90 (1.42–99.81)	0.023

TB, tuberculosis; ART, antiretroviral therapy; OR, odds ratio; 95% CI, 95% confidence interval.

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